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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,662	VANDEKERCKHOVE ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *9-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☒ Claim(s) *1, 8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/11/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-8 in the reply filed on 7/24/07 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 9-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/24/07 as discussed above.

3. Accordingly, claims 1-12 are pending, with claims 1-8 under examination.

Information Disclosure Statement

4. Applicant's Information Disclosure Statement filed 3/11/05 has been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached form PTO-1449.

5. Applicant is reminded that the listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

6. The disclosure is objected to because of the following informalities:

7. The specification contains drawings and/or flow diagrams on pages 27 and 29-33, which is improper because such descriptive illustrations should be presented separately as part of the drawings. The specification may contain chemical formulas and mathematical equations, *but must not contain drawings or flow diagrams*. See MPEP 608.01.

8. Applicant is also advised that the "Brief Description of the Drawings" in the specification should also be updated accordingly should the noted drawings be incorporated into the Drawings section.

9. The specification is objected to because the heading "BRIEF SUMMARY OF THE INVENTION," is not present. See MPEP § 608.01(a).

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.

(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

10. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 16. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Sequence Compliance

11. The specification is objected to for the following reasons:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1 .821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1 .821 through 1 .825 for the reason(s) set forth below.

It appears that while Applicant has successfully submitted sequences in a computer readable form, the specification is not compliant with sequence rules. For example, page 3, line 9 and page 34, lines 26 and 31 contain amino acid sequences that are not identified by SEQ ID numbers. This is not an exhaustive list.

Applicant is required to review the instant application for compliance with the

requirements of applications which contain sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825.

If the noted sequence(s) is in the sequence listing filed, Applicants must amend the specification to identify the sequence appropriately by SEQ ID NO. If the noted sequence(s) is not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g).

Applicant's time to comply with the sequence rules is set forth on the attached Office Action Summary (Form PTOL-326). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned.

Claim Objections

12. Claims 1 and 8 are objected to because of the following informalities:

13. Claim 1 refers to "**at least one target molecule**" in the preamble and in step (d); to "**at least one molecule**" interacting with the compound in part (a); and to "**compound-target**

complexes" in part (c) of the claim. Claim 6 also refers to "**the targets**". The use of the various different terms "target molecule", "molecule" and "target" in referring to the same species may cause confusion. Applicant is requested to employ consistent terminology throughout the claims.

14. Claim 8 recites "said identifying step based on the mass measuring of the target peptides", which is objected to because although claim 7 recites that the method may *be* "measurement of the mass of the peptides", it does not recite a method "**based on**" such a method.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

17. Claim 1 recites a method to isolate "at least one target molecule **of a compound**" (emphasis added). This language is vague and indefinite because it does not make clear the relationship of the target molecule to the compound—is the target molecule part of the compound? Or does the target molecule bind or interact with the compound"?

18. Claim 2 recites the limitation "the chromatographic conditions". There is insufficient antecedent basis for this limitation in the claims.

19. Claim 7 is indefinite in reciting improper overlapping Markush groups, such that the scope of the claim is unclear. Furthermore, it is unclear due the grammatical structure of the claim whether the clause "in combination with database searching" is meant to apply to all of the recited members of the Markush group, or alternatively only to the last member. In addition, the lack of an "and" or "or" conjunction concluding the Markush group also presents confusion.

20. Claim 7 is vague and indefinite in reciting, "in combination with database searching" because it is unclear what Applicant intends to encompass in the term "database search" as it is used in the claim. The specification does not provide a specific or limiting definition for "database searching". Does Applicant intend for the database search to encompass comparison of the isolated target molecules with known standards so as to obtain an identification of the proteins or peptides? If so, please clarify the claim accordingly.

21. Claim 8 recites the limitations "the determination of the number of free amino groups in the target peptides", "the knowledge about the cleavage specificity of the protease used to generate the protein peptide mixture" and "the grand average of the hydropathicity of the target proteins". There is insufficient antecedent basis for these limitations in the claims.

Furthermore, claim 8 is ambiguous in reciting "the knowledge about the cleavage specificity of the protease" because it is unclear what is encompassed in the term "knowledge" as used in the claim, and how the recited "knowledge" is obtained. The term "knowledge" as recited appears to be a subjective term that lacks a comparative basis for defining its metes and bounds. Does the term "knowledge" intend to encompass "standard values" or "reference" generally known about cleavage specificity of the proteases? Please clarify.

Claim Rejections - 35 USC § 102

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 1-2 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Cruickshank et al. ("Diagonal Chromatography for the Selective Purification of Tyrosyl Peptides", Canadian Journal of Biochemistry (1974) 52, 1013-17, of record).

Cruickshank et al. teach a method to isolate tyrosyl- or histidyl-containing peptides, comprising the steps of (a) adding a compound comprising a functional group that can be specifically altered (1-fluoro-2,4-dinitrobenzene, FDNB) to a complex mixture of molecules (carboxymethylated protein samples mixed with urea and other chemicals; see page 1014, right column) to form a compound-target complex (O-DNP-tyrosyl and DNP-histidyl-derivatized proteins, which are formed as a result of the reaction of FDNB with tyrosyl side chains to give the DNP group), (b) separating the resulting mixture by paper chromatography, (c) chemically altering the DNP compound by thiolysis, and (d) isolating at least one target molecule (tyrosine and/or histidyl-containing peptides) after DNP thiolysis by paper chromatography and final purification by electrophoresis. See entire selection, in particular the abstract; page 1013, right column to page 1015, right column, first paragraph; Figures 1-2; and page 1016, the paragraph bridging the left and right columns.

With respect to claim 2, both chromatographic steps were performed by paper chromatography and the second step was performed "under identical conditions" with the earlier

step (see page 1014, left column, "Experimental" and page 1015, "Isolation of Tyrosine-Containing Peptides", especially at the sentence bridging the left and right columns).

With respect to claim 6, the reference teaches identifying the sequence of isolated tyrosyl-containing peptides (page 1015, right column; and Table 1).

24. Claims 1-3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Creighton, T.E. ("Proteins: Structures and Molecular Properties" Second Edition, W.H. Freeman and Company, New York, 1993), page 41).

Creighton teaches diagonal techniques for the purification of proteins, in which peptides in a peptide mixture that contain a particular amino acid are selectively isolated in two electrophoretic or chromatographic steps, which are performed with an intervening step modification step that alters the mobilities of modified peptides. Specifically, the reference teaches (a) adding a compound (iodoacetic acid) to a complex mixture of peptides, wherein the iodoacetic acid covalently modifies cysteine residues to form carboxymethyl-Cys residues (see entire selection). The reference further teaches (b) performing a first separation step, which may be performed electrophoresis or by the more common HPLC analysis (page 41, right column, the second full paragraph; and left column, the first full paragraph). Subsequently, fractions are (c) modified with performic acid, which chemically alters the carboxymethyl-Cys residues to the sulfones (Eq. 1.84). When the peptides are (d) subjected to the same procedure a second time, modified peptides will be isolated as they lie off the diagonal (see left column, the second full paragraph).

Similar techniques can also be performed for chemical modification of other amino acids (page 41, right column).

Claim Rejections - 35 USC § 103

25. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

26. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

27. Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cruickshank et al.

Cruickshank et al. is as discussed above. The reference teaches contacting a compound (FDNB) with a complex mixture that includes carboxymethylated protein. See especially page 1014, "Carboxylation and Dinitrophenylation of Protein". Subsequently, the DNP-adducted protein is cleaved into fragments prior to chromatography (see especially pages 1014-1015, "Treatment of CM-Chymotrypsinogen and CM-Lysozyme". As a result of this proteolytic

cleavage step, a "protein peptide mixture" is formed that is comprised of the peptide cleavage products.

However, this method differs from that of the instant claims because the "complex mixture of proteins" is only formed *after* addition of the compound FDNB. As such, the compound is not added to the "protein peptide mixture" (proteolytically cleaved protein) but to the protein *per se* prior to cleavage.

The Courts have ruled that the selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results. See MPEP 2144.04.

In the instant case, it would have been obvious to one of ordinary skill in the art at the time of the invention to perform the proteolytic cleavage step prior to addition of the compound FDNB in the method of Cruickshank et al. because selection of any order of performing process steps constitute obvious variations of parameters and procedures that are routinely varied in the art. In this manner, one would arrive at the claimed invention because the proteolytically cleaved proteins would constitute a "protein peptide mixture" of fragments that would then be contacted with the FDNB.

28. Claims 3-5 and 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cruickshank et al. in view of Aebersold et al. (US 6,670,194) and Johansson et al. (US 6,716,589).

Cruickshank et al. is as discussed above. The reference differs from the invention of claims 3-5 as discussed immediately above. With respect to claims 7-8, Cruickshank et al. teach subsequent identification of the targets (tyrosyl- or histidyl-containing peptides) by amino acid

analysis (page 1015, right column), but fail to specifically teach identification by measuring the mass of the peptides in combination with database searching.

Aebersold et al. mass spectrometry-based methods for characterizing isolated peptides (the abstract). The reference teaches analysis of complex mixtures of proteins, i.e., those containing 5 or more distinct proteins or protein functions, digesting the protein sample with proteases to produce peptide fragments (column 3, lines 39-68; column 5, lines 33-60; column 12, lines 44-52). By isolating and analyzing the isolated peptide fragments, the presence of protein(s) in the sample can be determined since the peptides are characteristic of the originating protein (column 3, lines 39-68).

With respect to claim 4, Aebersold et al. also teach adding an affinity labeled reagent, which selectively reacts with certain groups that are typically found in proteins (e.g., sulfhydryl, amino, carboxy groups) (see column 5, lines 33-60). Such labeled reagents are added to the complex protein mixture, which is then cleaved into peptide fragments; peptide fragments that are labeled are then isolated and identified (ibid). This is analogous to the teachings in Cruickshank in which the affinity labeled reagent FDNB is added to the protein samples prior to their proteolytic cleavage (page 1014).

Aebersold et al. further teach "multiplexing", or analysis of multiple samples in a single analysis (see column 6, lines 40-45; column 7, lines 37-42). For example, sequence identification of multiple peptide components of a protein mixture can be obtained in a single analysis (see also heading to Table 2).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to perform the method of Cruickshank et al. using a complex mixture of

proteins as taught by Aebersold et al. (rather than a single protein) because Aebersold et al. taught that sequence identification of multiple peptide components can be obtained in a single analysis (such as that of Cruickshank et al.), thus providing an advantage by allowing for multiplexing, i.e. simultaneous analysis of multiple proteins at the same time. One would be motivated to do this in order to determine the presence of a protein or proteins in a complex mixture.

With respect to claim 4, Cruickshank et al. exemplify addition of the labeling reagent FDNB prior to proteolytic cleavage (page 1014, right column). Aebersold et al. also teach adding labeling reagents prior to proteolytic cleavage (column 5, lines 33-46). Therefore, when performing the method of Cruickshank et al. and Aebersold et al. on a complex mixture of proteins, it would have been further obvious to one of ordinary skill in the art at the time of the invention cleave the protein after reaction with the labeling reagent FDNB.

With respect to claims 7-8, Aebersold et al. teach that protein analysis has been revolutionized by the development of powerful mass spectrometric methods and the development of computer algorithms which correlate protein and peptide mass spectral data with sequence databases and thus rapidly and conclusively identify proteins (column 1, line 60 to column 2, line 8). Such methods can determine both the quantity and the sequence identity of tagged peptides. In particular, the sequence of isolated peptides in a complex mixture can be determined using tandem spectrometry techniques, and by application of sequence database searching techniques. Since the isolated peptide fragments are characteristic of the presence of the protein from which the sequenced peptide originated, in this manner the originating protein

can be identified and thus the presence of the protein in the complex mixture determined. See column 3, lines 39-68 and column 12, line 62 to column 13, line 25.

Johansson et al. also teach that as compared with amino acid analysis (the method used by Cruickshank et al.), mass spectrometry is more sensitive (column 11, lines 54-57).

Therefore, when performing the method of Cruickshank et al. and Aebersold et al., it would have been further obvious to one of ordinary skill in the art at the time of the invention to employ mass spectrometry (which is a mass measurement method) in combination with sequence database searching as taught by Aebersold et al. in place of the amino acid analysis method of Cruickshank et al.

One of ordinary skill in the art at the time of the invention would have been motivated to do this in order to identify the protein from which the sequenced peptide fragment originated, thereby allowing the presence of that protein in the mixture to be determined.

In particular, one would be motivated to substitute more recently-developed mass spectrometry-based techniques as taught by Aebersold et al. for the older methodology of amino acid analysis in order to achieve the same purpose, namely of determining the sequence identity of the tyrosine and/or histidyl-containing peptides. The teachings of Johansson et al. also establish that mass spectrometry was recognized in the art to be more sensitive than amino acid analysis.

One of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success because Aebersold et al. teaches that the mass spectrometric methods can identify the sequences of isolated and/or tagged peptides, which describes the tyrosyl- and histidyl-containing peptides that were identified in the method of Cruickshank et al.

With respect to claim 8, the method may be said to be "based on the knowledge about the cleavage specificity of the protease" since Cruickshank et al. teach that the proteases employed (pepsin, thermolysin, and elastase) cleaved the target proteins chymotrypsinogen and lysozyme. As such, given the broadest reasonable interpretation the methods may be said to be "based on" the knowledge that these proteases cleave the target proteins.

29. Claims 3-4 and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Creighton in view of Aebersold et al.

Creighton is as discussed above, which teaches a method substantially as claimed wherein peptides are purified from peptide mixtures.

The reference differs from the claimed invention of claim 4 with respect to the type of sample on which the method is performed. Specifically, Creighton fails to specifically teach adding the compound to a complex protein mixture that is then *cleaved* into a protein peptide mixture prior to separation step (b). Rather, in Creighton the compound is added to a protein peptide mixture; there is no specific teaching of a step in which the peptides are initially obtained by cleavage of proteins.

The reference also fails to specifically teach *identifying* the target peptides as in claims 6-8.

Aebersold et al. is as discussed above. The reference teaches that analysis of complex mixtures of proteins, i.e., those containing 5 or more distinct proteins or protein functions, can be achieved by analyzing isolated peptide fragments obtained by digestion or cleavage of the proteins in the sample mixture, typically with trypsin. See column 3, lines 39-68; and column 12,

lines 44-53. This allows for "multiplexing", or analysis of multiple samples in a single analysis (see column 6, lines 40-45; column 7, lines 37-42). For example, sequence identification of multiple peptide components of a protein mixture can be obtained in a single analysis (see also heading to Table 2).

Since the resulting peptide fragments are characteristic of the presence of the protein from which they originated, isolation and characterization of the peptide fragments can be used to determine the presence of the protein in the complex mixture (see also the abstract).

Therefore, with respect to claims 3-4, it would have been obvious to one of ordinary skill in the art at the time the invention was made perform the peptide purification method of Creighton on a sample that is a complex protein mixture, and to subsequently cleave the protein mixture into the peptide mixture from which peptides are isolated, in order to determine the presence of protein(s) in a complex mixture by purifying peptides obtained by protein digestion of the mixture. Motivation to modify the reference teachings in this manner comes from the teachings of Aebersold et al. that isolated peptide fragments can be used to identify the presence of the presence of the protein from which the peptides originated.

With respect to claim 4, Aebersold et al. also teach adding an affinity labeled reagent, which selectively reacts with certain groups that are typically found in proteins (e.g., sulfhydryl, amino, carboxy groups) (see column 5, lines 33-60). Such labeled reagents are added to the complex protein mixture, which is then cleaved into peptide fragments; peptide fragments that are labeled are then isolated and identified (ibid). The affinity labeled reagent of Aebersold et al., (which may react with sulfhydryl groups) is highly analogous to the iodoacetic acid modifying reagent of Creighton et al. that reacts with cysteine residues.

Therefore, it would have been further obvious to one of ordinary skill in the art at the time of the instant invention to add iodoacetic acid to the complex protein mixture and then cleave the protein mixture into a protein peptide mixture prior to separation when performing the method of Creighton and Aebersold et al. because Aebersold et al. exemplifies this order of performing the steps when analyzing a complex protein mixture sample. Furthermore, the Courts have ruled that the selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results. See MPEP 2144.04.

With respect to claims 6-8, Aebersold et al. teach that isolated peptides can be characterized by mass spectrometric techniques: in particular, the sequence of isolated peptides can be determined using tandem MS techniques, and by application of sequence database searching techniques, the protein from which the sequenced peptide can be identified (column 3, lines 54-60).

Therefore, when performing the peptide isolation method of Creighton on a complex protein mixture in order to identify proteins in the mixture according (as taught by Aebersold et al.), it would have been further obvious to one of ordinary skill in the art at the time of the instant invention to identify the isolated peptides by mass spectrometry in combination with sequence database searching as taught by Aebersold et al. because Aebersold et al. taught that isolated peptides can be sequenced and characterized by mass spectrometry in this manner, thereby allowing identification of the protein from which they originate, and consequently allowing for determination of the presence of that protein in the complex mixture.

With respect to claim 8, Aebersold et al. teach the protease trypsin for protein digestion (column 12, lines 44-53). It is implicit from this teaching that trypsin is known to cleave

proteins. Therefore, when employing trypsin to produce the peptide fragments according to the method of Creighton and Aebersold et al., such a method would be said to take into account the "knowledge about the cleavage specificity of the protease" given the broadest reasonable interpretation of this terminology.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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